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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/393,795	09/10/99	GRAY J	CMCC693P2A

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EXAMINER	
LEFFERS JR,G	
ART UNIT	**PAPER NUMBER**
1636	8

DATE MAILED: 02/15/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/393,795	Applicant(s) Gray, et al.
	Examiner Gerald G. Leffers Jr.	Group Art Unit 1636

☐ Responsive to communication(s) filed on _____ .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-49* is/are pending in the application.

Of the above, claim(s) *4, 6, 11, 15, 19, 21, 26, 30, 34, and 38-49* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-3, 5, 7-10, 12-14, 16-18, 20, 22-25, 27-29, 31-33, and 35-37* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *7*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Election/Restriction

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-3, 5, 7-10, 12-14, 16-18, 20, 22-25, 27-29, 31-33 and 35-37, drawn to methods of making packaging cell lines, packaging cell lines and particles made by the packaging cell lines, classified in class 435, subclasses 320.1, 325, 455 and 465; class 536, subclass 23.1.

II. Claims 39-43, drawn to isolated nucleic acids, classified in class 435, subclass 320.1; class 536, subclass 23.1.

III. Claims 4, 6, 11, 15, 19, 21, 26, 30, 34, 38 and 44-46, drawn to *in vivo* methods introducing a coding sequence into a mammal, classified in class 424, subclass 93.2; class 435, subclass 456.

IV. Claims 4, 6, 11, 15, 19, 21, 26, 30, 34, 38 and 47-49, drawn to *ex vivo* methods of introducing a coding sequence into a mammal, classified in class 424, subclass 93.21; class 435, subclass 456.

The inventions are distinct, each from the other because of the following reasons:

Inventions of Groups I and II are related as subcombinations disclosed as usable together in a single combination. The subcombinations are distinct from each other if they are shown to

be separately usable. In the instant case, the isolated nucleic acids of Group II are separately usable such as a source of viral sequences for PCR amplification and subsequent subcloning. See MPEP § 806.05(d).

The recombinant lentivirus particles of Group I and the inventions of Groups III-IV are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the packaged viral particles of Group I can be used in the methods of Group III and Group IV. Also, the methods of Group I are biologically and functionally different and distinct from those of Groups III-IV and one does not render the other obvious. The methods of Group I and Groups III-IV comprise steps which are not required for or present in the methods of the other groups: transfection of host cells with plasmid DNAs (Group I) and infection of host cells *in vivo* (Group III) or *ex vivo* (Group IV) with recombinant lentivirus. The end result of the methods are different: construction of packaging cell lines and packaging of recombinant lentivirus (Group I) and gene therapy mediated treatment of a living organism (Groups III-IV).

The inventions of Group II and Groups III-IV are biologically and functionally different and distinct from each other and thus one does not render the other obvious. The isolated nucleic acid of Group I is not used in the methods of Groups III-IV. The operation, function and effects of the isolated nucleic acids of Group II (to encode viral proteins needed for viral packaging in

packaging cell lines) are completely distinct and different from the operation, function and effects of the methods of Groups III-IV which result in the delivery of target nucleic acids to the cells of a living organism. Therefore, the inventions of theses different, distinct groups are capable of supporting separate patents.

The inventions of Groups III and IV are biologically and functionally different and distinct from each other and thus one does not render the other obvious. The methods of Groups III-IV comprise steps which are not required for or present in the methods of the other group: infection of cells within an organism (Group III) and infection of cells taken from an organism and return of infected cells to the organism (Group IV). The cell populations amenable to the approach of one method may not be amenable to the approach of the other method and thus the different methods are likely to effect different target cell populations within the organism. Thus, the operation, function and effects of these different methods are different and distinct from each other. Therefore, the inventions of these different, distinct groups are capable of supporting separate patents.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, restriction for examination purposes as indicated is proper.

During a telephone conversation with David Brook on 2/9/2000 a provisional election was made with traverse to prosecute the invention of Group I, claims 1-3, 5, 7-10, 12-14, 16-18, 20, 22-25, 27-29, 31-33 and 35-37. Affirmation of this election must be made by applicant in

replying to this Office action. Claims 4, 6, 11, 15, 19, 21, 26, 30, 34, and 38-49 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(I).

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 5, 7-10, 12-14, 16-18, 20, 22-25, 27-29, 31-33 and 35-37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 8, 12, 16, 23, 27, 31 and 35 are vague and indefinite in that the phrase "..for producing a viral accessory protein independent .." is only an intended use for the packaging cell lines which has little patentable weight because the rest of the claim stands on its own. It woud be remedial to amend the claim language to indicate that production of viral accessory protein

independent particles is an actual property of the cell lines and not just an intended use for the cell lines.

Claims 1, 8, 12, 16, 23, 27, 31 and 35 are vague and indefinite in that the metes and bounds of the phrase "..accessory protein independent .." are unclear. Does this limitation mean that no accessory protein coding sequences for the lentivirus are present or expressed? Or does the limitation mean that only one or more accessory protein sequences are not present or expressed? Upon reading the specification it appears applicants intend the limitation to specify that no accessory proteins are present or expressed in the claimed packaging systems and that no constitutively expressed transport elements (CTEs) are to be expressed either (page 9, line 17). However, the inclusion of Figure 3 in the specification in which a three plasmid system for packaging HIV-1 particles is featured, and which clearly allows expression of most of the accessory proteins (but not *vpu*), seems to indicate that the phrase refers to systems where only some of the accessory proteins are not present or expressed. There does not appear to be any clear indication in the specification that the three plasmid system taught by Naldini et al (AR) and shown schematically in Figure 3 is not the same system claimed by the instant specification. It would be remedial to amend the claims to indicate clearly that the phrase "..accessory protein independent.." means that no accessory protein genes are present or expressed and that no constitutively expressed transport elements (CTEs) are to be expressed either.

Claims 1, 5, 7-8, 12, 16, 20, 22-23, 27, 31 and 35 are vague and indefinite in that the metes and bounds of the phrase "..mutagenized to improve expression.." are unclear. Would

only a single base-pair change within the coding region for *gagpol* with the intent of improving expression satisfy the limitation intended by the phrase? Would changes made to the regulatory sequences associated with *gagpol* be encompassed by the claim language? Upon what basis would the change have to be made in order to satisfy the limitation of improving expression? Also, what is the baseline for determining improvement in gagpol expression? How does what is claimed differ from other variants of *gagpol* in the art which have higher expression for gag and pol than still other variants? It would be remedial to specify exactly what type and degree of changes to *gagpol* are encompassed by the phrase "..mutagenized to improve expression.." and to indicate what is considered the baseline for expression of *gagpol*.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 5, 7-10, 12-14, 16-18, 20, 22-25, 27-29, 31-33 and 35-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Naldini et al (AR) in view of Haas et al (AV).

Naldini et al teach the desirability of developing an HIV-based retroviral packaging system for the purpose of infecting non-proliferating cells which can not be infected by other,

non-lentivirus systems (page 263, column 1). Naldini et al teach the use of a three plasmid system to generate packaging cell lines featuring a first plasmid comprising *gagpol* sequences from HIV-1, a second plasmid comprising a gene encoding a heterologous envelope protein, and a third plasmid encoding an RNA packaging substrate bearing all of the cis-acting elements required for packaging, reverse transcription, and integration into the host genome as well as restriction sites for introduction of a coding sequence for a protein of interest (page 263, Figure 1). Naldini et al teach that all of the accessory protein sequences except for *vpu* are expressed in this system (page 263, column 1). Naldini et al teach the use of the genes for MLV amphotropic envelope protein or the vesicular stomatitis virus G glycoprotein (VSV G) to pseudotype the recombinant viral particles produced by the HIV-based three-plasmid packaging system in order to increase the range of target cells which can be infected by the particles produced by this system (column 2, page 263).

Naldini et al do not specifically teach mutagenesis of the *gagpol* coding region in order to improve expression of the two proteins.

Haas et al teach that poor expression of envelope proteins limits the titre of retroviral pseudotypes, suggesting that better expression of the envelope protein in packaging cell lines would result in higher titres of particles bearing the heterologous envelope protein. Haas et al also teach that the *env* gene of HIV-1 has a very pronounced codon bias that apparently, in addition to other regulatory factors, limits expression of the *env* gene. Haas et al also teach that this pronounced codon bias also extends to the *gag* and *pol* genes (page 315, column 2). Haas et

al teach that mutating the HIV-1 *env* coding sequence by altering the codon usage for *env* to more closely reflect the codon preference for highly expressed human genes, while still maintaining the wildtype env amino acid sequence, results in much higher levels of expression for the HIV-1 env protein from cytoplasmically transcribed DNA (page 316, columns 1 & 2; page 317, columns 1 & 2; Figure 3). Haas et al teach that the increased levels of env protein do not appear to be due to increased levels of nuclear export for the mRNA since transcription occurred in the cytoplasm and that increased levels of RNA also do not account for the increased level of protein (page 317, column 2; Figure 6). Haas et al teach that the codon usage for the env proteins of other lentiviruses is strikingly similar in that in all cases the preferred codon for HIV-1 is the same for the other lentiviruses (page 320, column 2).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the three plasmid system for generating HIV-based packaging cell lines and packaging recombinant HIV-1 particles as taught by Naldini et al to include mutagenesis of the HIV structural genes as taught by Haas et al because Naldini et al teach the efficacy of the three plasmid approach for producing high titre stocks of recombinant HIV-1 particles and because Haas et al teach that it is within the ordinary skill of the art to mutagenize coding sequences for the structural genes of lentiviruses to more closely reflect the codon usage of genes highly expressed in human cells and, consequently, result in dramatically increased levels of production of the HIV structural genes. One would have been motivated to do so in order to receive the

expected benefit of generating increased amounts of the gag, pol and envelope components of the recombinant HIV-1 particles, thus generating higher titres of the HIV particles from the packaging cell lines, as suggested by Haas et al. Absent any evidence to the contrary there would have been a reasonable expectation of success in using the packaging system made from the combined teachings above to generate even higher titres of recombinant lentivirus particles for use in gene delivery methods in which a higher multiplicity of infection is desirable.

Conclusion

No claims are allowed.

Certain papers related to this application may be submitted to Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald Leffers, Jr. whose telephone number is (703) 308-6232. The examiner can normally be reached on Monday through Friday, from about 8:00 AM to about 4:30 PM. A phone message left at this number will be responded to as soon as possible (usually no later than 24 hours after receipt by the examiner).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. George Elliott, can be reached on (703) 308-4003.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

GGL

G. Leffers, Jr.

Patent Examiner

Art Unit 1636

TERRY MCKELVEY
PRIMARY EXAMINER

February 11, 2000